REMARKS/ARGUMENTS

Upon entry of this amendment, claims 1-9 and 11-22 will be pending in the present application. Claims 10 and 23-56 are canceled herein without prejudice to prosecution of the subject matter contained therein at a later date. Claims 11-22 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1 and 11 are amended herein. The specification is amended herein to remove embedded hyperlinks. No new matter has been introduced by way of this amendment.

Applicants' invention provides a novel method for synthesizing a polynucleotide having a target nucleotide sequence by coupling oligonucleotides sharing terminal regions of sequence and assembling the polynucleotide by extension of the coupled oligonucleotides.

I. Rejoinder of claims 11-22 is proper.

Applicants traverse the requirement for restriction for the reasons of record. Nonetheless, Applicants have amended claim 11 to depend from claim 1. Applicants assert that no undue search burden upon the Examiner will be generated by rejoinder of claims 11-22 as amended herein. Accordingly, Applicants respectfully request rejoinder and consideration on the merits of claims 11-22.

II. Claims 1-9 satisfy 35 U.S.C. § 112, second paragraph.

Claims 1-9 are rejected under 35 U.S.C. § 112, second paragraph for alleged indefiniteness. Applicants traverse the rejection.

Claim 1 is rejected for alleged indefiniteness in the recitation of the term "coupling." Applicants respectfully assert, however, that the term coupling is sufficiently and clearly

defined in the specification to inform the ordinarily skilled artisan of the metes and bounds of the present invention. "Coupling" is defined in the specification on page 10, lines 4-6, as the covalent joining of two molecules. In the case of coupling of oligonucleotides, coupling preferably refers to the covalent joining of oligonucleotides at their ends to form a linear coupled oligonucleotide. As illustrated in Figures 1 and 2 of the specification, coupling may occur at the 5' or 3' end of an oligonucleotide to be coupled depending upon the sequence of the target polynucleotide being synthesized. In other words, assembly of the oligonucleotides may occur 5'→ 3' or 3'→ 5'.

Claim 1 is further rejected for alleged indefiniteness in the recitation of "region of the polynucleotide." Applicants traverse. A person having ordinary skill in the art would understand that phrase to refer to the nucleotide sequence of the target polynucleotide being synthesized. Nonetheless, to advance prosecution of the application, Applicants have amended claim 1 to recite "region of sequence of the polynucleotide." The length and sequence of the polynucleotide represented by the coupled oligonucleotides is irrelevant to conveying the metes and bounds of the invention to one having ordinary skill in the art. Indeed, one of the advantages of the present invention is the versatility it allows in the generation of polynucleotides of varying size and sequence.

Claim 1 also is rejected as allegedly indefinite in the recitation of "terminal region of sequence." Applicants disagree. The terminal region of sequence of the coupled oligonucleotide can refer to a portion of the sequence of the coupled oligonucleotide at either its 5' or 3' terminus depending upon the sequence of the target polynucleotide being synthesized, as illustrated in Figures 1 and 2 of the specification.

Applicants respectfully submit that claims 1-9 comply with the requirements of 35 U.S.C. § 112, second paragraph.

II. Claims 1, 2, 4-6, 8, and 9 are patentable over U.S. Patent No. 6,506,594 to Barany *et al.*

Claims 1, 2, 4-6, 8, and 9 of the invention are rejected for alleged anticipation under 35 U.S.C. § 102(e). Applicants disagrees.

To anticipate a claim, a prior art reference must teach, either expressly or inherently, each and every element of the claim. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

The rejected claims are directed to methods of preparing polynucleotides having target sequences from a plurality of oligonucleotides by coupling the oligonucleotides to form a plurality of coupled oligonucleotides, each representing a region of the target polynucleotide sequence and each sharing at least one terminal region of sequence with another coupled oligonucleotide, and assembling the polynucleotide by extension of the coupled oligonucleotides.

In contrast to the presently claimed methods, U.S. Patent No. 6,506,594 to Barany *et al.* (Barany) describes a ligase detection reaction for identifying nucleic acid sequence differences. The methods of Barany include a ligation phase, a capture phase, and a detection phase. In the ligation phase, a first oligonucleotide probe having a target-specific sequence and an "addressable array-specific" portion and a second oligonucleotide probe having a target-specific sequence and a detectable reporter label are hybridized to the target sequence. When the two probes hybridize to the target sequence adjacent to one another and no

interfering mismatch is present, ligation of the probes occurs in the presence of a ligase. The capture phase involves hybridization of the addressable array-specific portions of the first probe to complementary capture oligonucleotides bound to solid support. Detection of the presence of the reporter label on the solid support indicates the presence of a sequence in the sample. (Barany, column 10, line 14 to column 11, line 7.)

Barany does not teach that the ligated oligonucleotides share a terminal region of sequence with another ligated oligonucleotide. Additionally, Barany describes amplification of the target polynucleotide sequence prior to the ligation reaction in order to increase the quantity of target nucleotide sequence. (Barany, column 14, lines 13 to 62.) However, no extension of the oligonucleotide probes to arrive at the target polynucleotide, as presently claimed, is taught by the reference. In other words, the Barany reference simply describes a method of detection of a target polynucleotide sequence, not a method of synthesis of a target polynucleotide sequence as presently claimed.

As Barany does not teach each limitation of rejected claims 1, 2, 4-6, 8, and 9, that reference cannot anticipate the present invention as defined by those claims. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 4-6, 8, and 9 over Barany.

III. Claims 1, 2, 4, and 5 are patentable over U.S. Patent No. 6,495,318 to Harney *et al.*

Claims 1, 2, 4, and 5 are rejected for alleged anticipation by U.S. Patent No. 6,495,318 to Harney *et al.* (Harney). Applicants disagree with the rejection.

Harney describes methods for producing multicomponent nucleic acid constructs. The Harney methodology relies on the annealing of nucleic acid components of the construct having single stranded complementary overhangs and linkage of the annealed components. (Harney, column 9, lines 25-58). In contrast, synthesis of polynucleotides by the presently claimed methods relies on covalent linkage of oligonucleotides to yield coupled oligonucleotides having at least one shared terminal region of sequence, as distinguished from regions of complementary sequence taught by Harney, with at least one other coupled oligonucleotide, followed by extension of the coupled oligonucleotides. Harney fails to teach, either expressly or inherently, one or more shared regions of terminal sequence of the coupled oligonucleotides.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 2, 4, and 5 based on Harney.

IV. Claims 1, 4, 5, 7, and 8 are patentable over U.S. Patent No. 6,489,466 to Huang *et al.*

Claims 1, 4, 5, 7, and 8 are rejected for alleged anticipation by U.S. Patent No. 6,489,466 to Huang *et al.* (Huang). Applicants disagree with the rejection.

Huang describes a method for oligonucleotide synthesis involving tethering a nucleotide monomer or polymer having a modified 5'-terminus and a protected 3'-terminus to a solid support; removing the 3' protecting group; activating the 3'-terminus of the tethered base by the addition of a phosphoramidite moiety; and coupling the activated 3'-terminus to a the 5'-terminus of a 3'-protected nucleotide. (Huang, column 9, line 31 to column 10, line 18 and Figure 4.) Huang fails to teach, either expressly or inherently, that the coupled

oligonucleotides share at least one terminal region of sequence with at least one other coupled oligonucleotide, as presently claimed. Applicants respectfully submit that Huang does not anticipate claims 1, 4, 5, 7, and 8 and, accordingly, request reconsideration and withdrawal of the rejection.

V. Claims 1-5 and 7-9 are patentable over U.S. Patent No. 6,479,262 to Delagrave.

Claims 1-5 and 7-9 are rejected under 35 U.S.C. § 102(e) for alleged anticipation by U.S. Patent No. 6,479,262 to Delagrave (Delagrave). Applicants traverse the rejection.

Delagrave teaches methods of synthesis of polynucleotides by sequential ligation of oligonucleotide segments. (Delagrave, Figures 1 and 2.) The Delagrave patent, however, does not teach that the coupled oligonucleotides share at least one terminal region of sequence with at least one other coupled oligonucleotide. Thus, Delagrave does not anticipate claims 1-5 and 7-9.

Applicants respectfully request reconsideration and withdrawal of the rejection.

VI. Claims 1-6 and 8-9 are patentable over Barany in view of Walker *et al.*

Claims 1-6 and 8-9 are rejected under 35 U.S.C. § 103 for alleged obviousness over Barany in view of Walker *et al.* (*PNAS*, 1975, 72(1):122-126) (Walker). Applicants disagree with the rejection.

To establish a *prima facie* case of obviousness, three requirements must be satisfied: first, there must be some suggestion or motivation to modify the reference or to combine the reference teachings; second, there must be a reasonable expectation of success for achieving

the claimed invention and its particular results; and, third, the prior art references must teach or suggest all the claim limitations. *See In re Vaeck*, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991).

As previously noted, the methods of Barany include a ligation phase, a capture phase, and a detection phase. In the ligation phase, a first oligonucleotide probe having a target-specific sequence and an "addressable array-specific" portion and a second oligonucleotide probe having a target-specific sequence and a detectable reporter label are hybridized to the target sequence. When the two probes hybridize to the target sequence adjacent to one another and no interfering mismatch is present, ligation of the probes occurs in the presence of a ligase. The capture phase involves hybridization of the addressable array-specific portions of the first probe to complementary capture oligonucleotides bound to solid support. Detection of the presence of the reporter label on the solid support indicates the presence of a sequence in the sample. (Barany, column 10, line 14 to column 11, line 7.)

Barany does not teach that the ligated oligonucleotides share a terminal region of sequence with another ligated oligonucleotide. Additionally, Barany describes amplification of the target polynucleotide sequence prior to the ligation reaction in order to increase the quantity of target nucleotide sequence. (Barany, column 14, lines 13 to 62.) However, no extension of the oligonucleotide probes to arrive at the target polynucleotide, as presently claimed, is taught by the reference. In other words, the Barany reference simply describes a method of detection of a target polynucleotide sequence, not a method of synthesis of a target polynucleotide sequence as presently claimed.

Walker does not bridge the gap between the deficiencies in the Barany disclosure and the presently claimed method of polynucleotide synthesis. Walker makes no mention of

regions of shared sequence or extension of the coupled oligonucleotides to yield the target polynucleotide.

As the combination of Barany and Walker does not amount to the presently claimed invention, Applicants submit that claims 1-5 and 7-9 are nonobvious. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

VII. Claims 1 and 4-9 are patentable over Huang in view of Harney.

Claims 1 and 4-9 are rejected under 35 U.S.C. § 103 for alleged obviousness over Huang in view of Harney. Applicants traverse the rejection.

Huang describes a method for oligonucleotide synthesis involving tethering a nucleotide monomer or polymer having a modified 5'-terminus and a protected 3'-terminus to a solid support; removing the 3' protecting group; activating the 3'-terminus of the tethered base by the addition of a phosphoramidite moiety; and coupling the activated 3'-terminus to a the 5'-terminus of a 3'-protected nucleotide. (Huang, column 9, line 31 to column 10, line 18 and Figure 4.) There is no disclosure in Huang, however, of one or more shared terminal regions of sequence of a coupled oligonucleotide with at least one other coupled oligonucleotide, as presently claimed.

Harney describes methods for producing multicomponent nucleic acid constructs. The Harney methodology relies on the annealing of nucleic acid components of the construct having single stranded complementary overhangs and linkage of the annealed components. (Harney, column 9, lines 25-58). Like Huang, Harney fails to teach, either expressly or inherently, one or more shared regions of terminal sequence of the coupled oligonucleotides.

Since the combined teaching of the cited references fails to amount to the present invention as defined by solicited claims 1 and 4-9, Applicants respectfully request reconsideration and withdrawal of the rejection.

VIII. The obviousness-type double patenting rejection of claims 1-5 and 7-8 over Delagrave is improper.

Claims 1-5 and 7-8 are rejected for alleged obviousness-type double patenting in view of claims 1, 7, 10, 12, 14, 18, and 24-26 of Delagrave. Applicants disagree.

The doctrine of double patenting seeks to prevent the unjustified extension of patent exclusivity beyond the term of a patent. (MPEP § 804.) Nonstatutory-type double patenting rejections are based on a judicially created doctrine grounded in public policy primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent which are not patentably distinct from claims in a first patent. In determining whether a nonstatutory basis exists for a double patenting rejection, the issue is whether any claim in the application defines an invention that is merely an obvious variation of an invention claimed in a patent. (MPEP § 804 II.B.1.) The analysis parallels that for a 35 U.S.C. § 103 obviousness rejection. (*Id.*)

The methods of Delagrave relate to synthesis of polynucleotides by sequential ligation of oligonucleotide segments. (Delagrave, Figures 1 and 2.) The Delagrave patent, however, does not teach that the coupled oligonucleotides share at least one terminal region of sequence with at least one other coupled oligonucleotide. This element of the solicited claims is more than a mere obvious variation over claims 1, 7, 10, 12, 14, 18, and 24-26 of Delagrave. As such, claim 1-5 and 7-8 are patentably distinct over the recited claims of Delagrave.

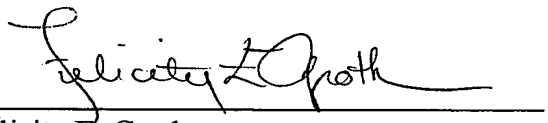
Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a Notice of Allowance at an early date is respectfully requested

If the Examiner believes a telephone conference would expedite prosecution of this application, the undersigned may be contacted at 215-557-5908.

Respectfully submitted,



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